ACC.12
61st Annual Scientific Session & Expo
ACC-i2 with TCT innovation in intervention

E573
JACC March 27, 2012
Volume 59, Issue 13

Arrhythmias

EVALUATION OF RECOMBINANT ACTIVATED FACTOR VII, PROTHROMBIN COMPLEX CONCENTRATE AND FIBRINOGEN CONCENTRATE TO REVERSE APIXABAN IN A RABBIT MODEL

ACC Oral Contributions
McCormick Place North, N426
Sunday, March 25, 2012, 9:03 a.m.-9:15 a.m.

Session Title: Management of the Patient with Atrial Fibrillation: Anticoagulation and Prevention of Stroke-- Joint Oral Arrhythmias Session of the Heart Rhythm Society and the American College of Cardiology
Abstract Category: 20. Arrhythmias: Other
Presentation Number: 904-8

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Background: As a potent anticoagulant agent, apixaban exposes to a risk of bleeding. An effective way to reverse its effects is needed. Objectives were to study efficacy and safety of recombinant activated factor VII (rFVIIa), prothrombin complex concentrate (PCC) and fibrinogen concentrate to reverse the anticoagulant effect of apixaban in a rabbit model of bleeding and thrombosis.

Methods: First, a dose ranging study assessed the minimal apixaban dose that increased bleeding. Then, 63 anaesthetized and ventilated rabbits were randomized into 5 groups: control (saline), apixaban (apixaban and saline), rFVIIa (apixaban and rFVIIa), PCC (apixaban and PCC) and fibrinogen (apixaban and fibrinogen). The Folts model was applied: a stenosis and an injury were carried out on the carotid artery, inducing thrombosis, detected as cyclic flow reductions, which were recorded over 20 minutes. Then the following were measured: ear immersion bleeding time, clotting times, anti-Xa activity, thrombelastometric parameters and thrombin generation test (TGT). Ultimately, a hepatosplenic section was performed and the total amount of blood loss after 15 min was evaluated as primary end point.

Results: Apixaban increased blood loss (12[9-14]g vs. 8[5,5-11]g for control (median [range]), $p<0.0003$), lengthened ear bleeding time, Prothrombin Time (PT), thrombelastographic clotting time and decreased thrombin generation. rFVIIa decreased ear bleeding time (81[70-100] s vs 118[106-154]s, $p<0.05$), but without efficacy on blood loss. PCC and rFVIIa decreased PT as well as thrombelastographic clotting time and shortened the lag time in TGT. Fibrinogen concentrate, surprisingly, increased blood loss and BT whereas it improved thromboelastographic clot firmness and increased thrombin generation to supraphysiological levels. Regarding safety, neither rFVIIa, PCC nor fibrinogen concentrate increased cyclic flow reductions.

Conclusion: rFVIIa, PCC and fibrinogen concentrate improved laboratory parameters, but did not reverse apixaban induced-bleeding.